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Background

- Women have nearly twice the lifetime risk of Alzheimer's disease (AD) compared to men¹
- This increased risk extends beyond longevity, and emerging evidence suggests that neuroendocrine factors contribute to this increased vulnerability^{2,3}
- Women show greater tau burden/accumulation, especially with high β -amyloid ($A\beta$)³⁻⁶
- Yet, whether midlife reproductive-endocrine factors influence tau pathology, and whether this depends on $A\beta$ burden, remains unknown

Aim

- To examine associations between reproductive-endocrine factors and tau burden/accumulation, accounting for $A\beta$ burden, across pooled female aging cohorts
- To estimate population attributable fractions for AD biomarker positivity associated with reproductive-endocrine factors

Methods

Multi-Cohort data

Characteristic	N	WRAP N = 322	BLSA N = 71	HABS-HD N = 656	HEAD N = 184	NACC FTP N = 378	NACC MK N = 283	PREVENT AD N = 160
Age at tau PET	2,054	67.3 ± 6.9 (48.0, 82.0)	75.9 ± 8.0 (57.0, 91.0)	66.1 ± 8.3 (49.0, 90.0)	66.4 ± 8.7 (22.0, 85.0)	68.8 ± 7.4 (48.0, 87.0)	64.8 ± 8.4 (41.0, 87.0)	67.7 ± 4.8 (59.0, 81.0)
Education	1,869	16.2 ± 2.8 (11.0, 29.0)	17.9 ± 2.4 (12.0, 21.0)	13.5 ± 3.8 (0.0, 20.0)		15.8 ± 2.7 (3.0, 23.0)	16.0 ± 2.5 (8.0, 21.0)	15.4 ± 3.3 (7.0, 24.0)
Amyloid Positive	2,054	88 / 322 (27.3%)	19 / 71 (26.8%)	122 / 656 (18.6%)	50 / 184 (27.2%)	140 / 378 (37.0%)	68 / 283 (24.0%)	42 / 160 (26.3%)
MTL SUVR	2,054	1.0 ± 0.3 (0.6, 2.5)	1.1 ± 0.1 (0.8, 1.7)	1.1 ± 0.1 (0.8, 2.1)	1.1 ± 0.2 (0.9, 2.8)	1.3 ± 0.2 (0.8, 2.2)	1.0 ± 0.3 (0.5, 2.7)	1.1 ± 0.1 (0.9, 1.8)
Menopause age	561	50.4 ± 5.8 (29.0, 60.0)	49.2 ± 5.1 (34.0, 59.0)		49.5 ± 5.1 (33.0, 63.0)			49.3 ± 5.0 (31.0, 60.0)
Menopause type (Surgical)	1,330	78 / 297 (26.3%)	12 / 64 (18.8%)	194 / 635 (30.6%)	30 / 174 (17.2%)			19 / 160 (11.9%)
Hormone therapy (HT) use	2,010	162 / 283 (57.2%)	42 / 70 (60.0%)	75 / 652 (11.5%)	68 / 184 (37.0%)	51 / 378 (13.5%)	40 / 283 (14.1%)	94 / 160 (58.8%)
HT delay (years from menopause)	219	0.0 ± 8.2 (-31.0, 30.0)	-1.5 ± 6.6 (-18.0, 20.0)		-1.4 ± 6.6 (-21.0, 31.0)			-1.3 ± 5.0 (-16.0, 10.0)
Hysterectomy	1,127	102 / 322 (31.7%)	19 / 71 (26.8%)	192 / 390 (49.2%)	44 / 184 (23.9%)			37 / 160 (23.1%)
Oophorectomy (Bilateral)	1,371	62 / 319 (19.4%)	12 / 71 (16.9%)	155 / 641 (24.2%)	21 / 182 (11.5%)			19 / 158 (12.0%)

¹ Mean ± SD (Min, Max); n / N (%)

Statistical Analyses:

Continuous associations between reproductive-endocrine factors and tau burden were assessed using general linear models/linear mixed-effects models, adjusting for age at tau PET and cohort. Interaction models tested whether $A\beta$ burden modified these associations.

Population attributable fractions (PAFs) for reproductive-endocrine factors were estimated for A+, T+, and A+T+ status using cohort-specific cut-offs derived from a reference group (<75 years, CL <20). A+ = CL ≥20; T+ = MTL SUVR >2 SD above reference group.

References

- Alzheimer's Association Report, 2022/2024
- Coughlan et al., JAMA Neurology, 2023
- Coughlan et al., JAMA Neurology, 2025
- Buckley et al., JAMA Neurology, 2019
- Buckley et al., Annals Neurology, 2020
- Coughlan et al., JAMA Neurology, 2026

Collaborators

BLSA Baltimore Longitudinal Study of Aging

HEAD STUDY

HEALTH & AGING BRAIN STUDY

NACC National Alzheimer's Coordinating Center

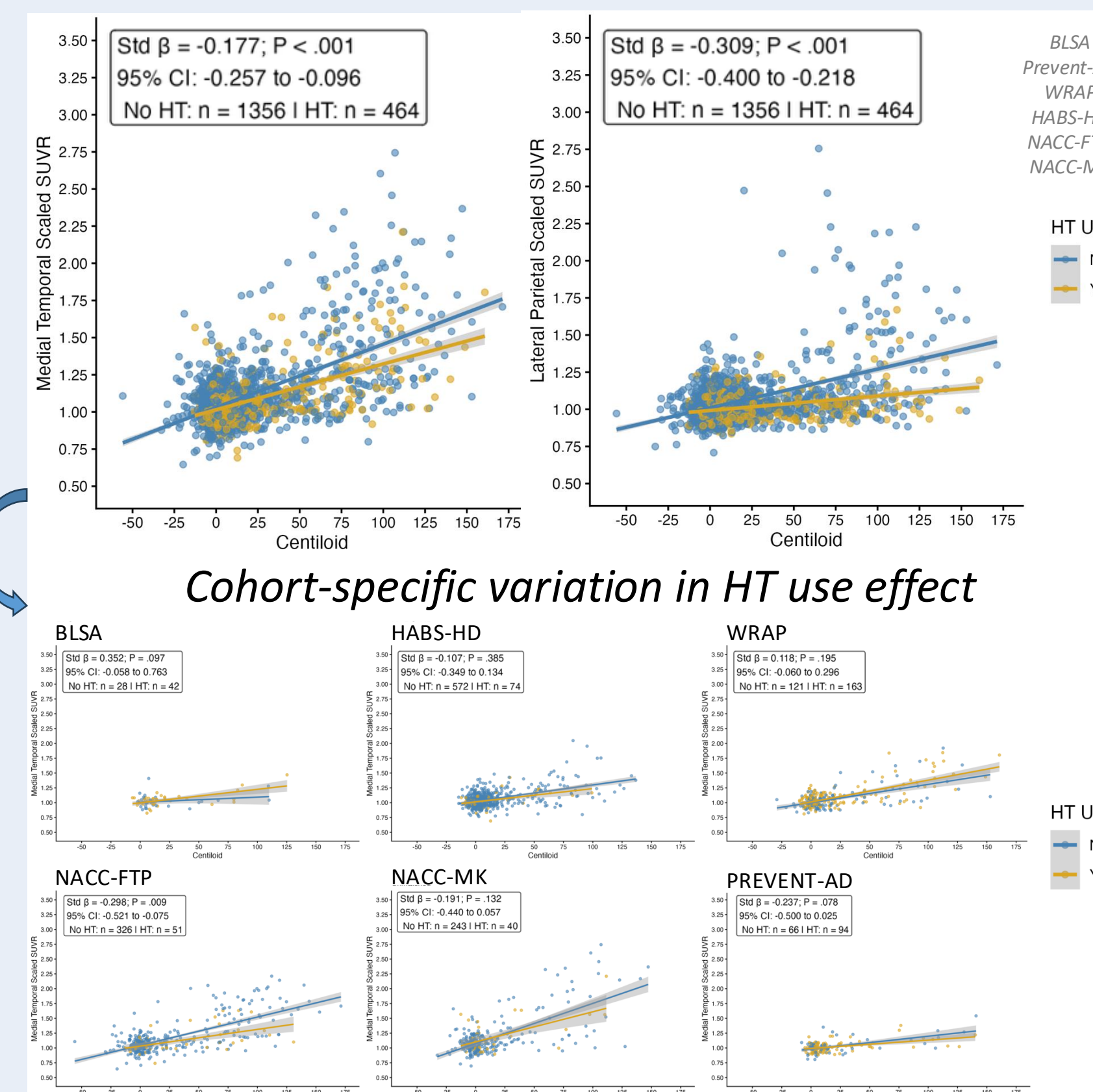
PREVENT-AD Research Group

Wisconsin Registry for Alzheimer's Prevention

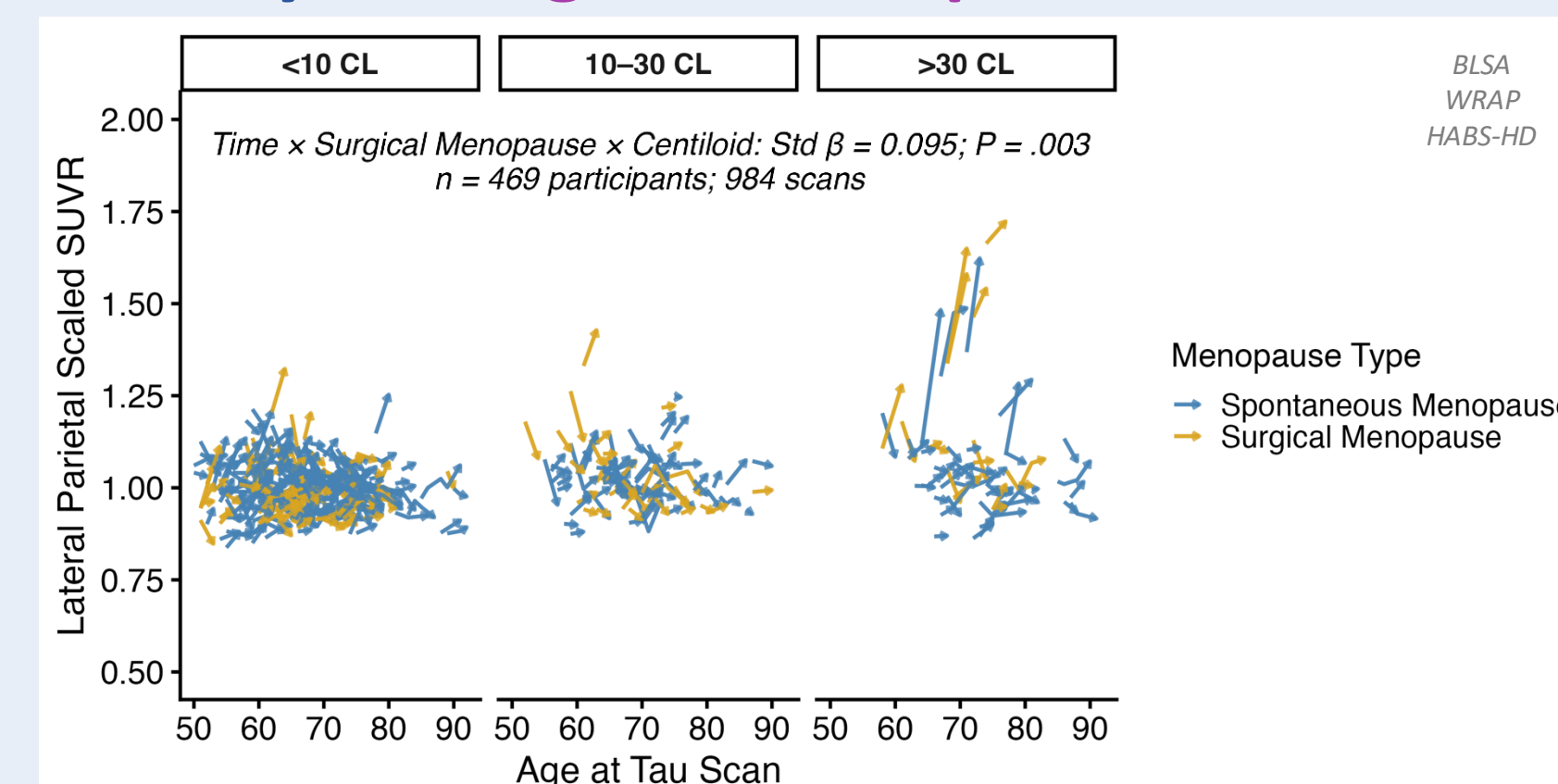
Project: leap^w care

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1. In those with higher amyloid levels, hormone therapy (HT) use associated with lower MTL and LP tau burden

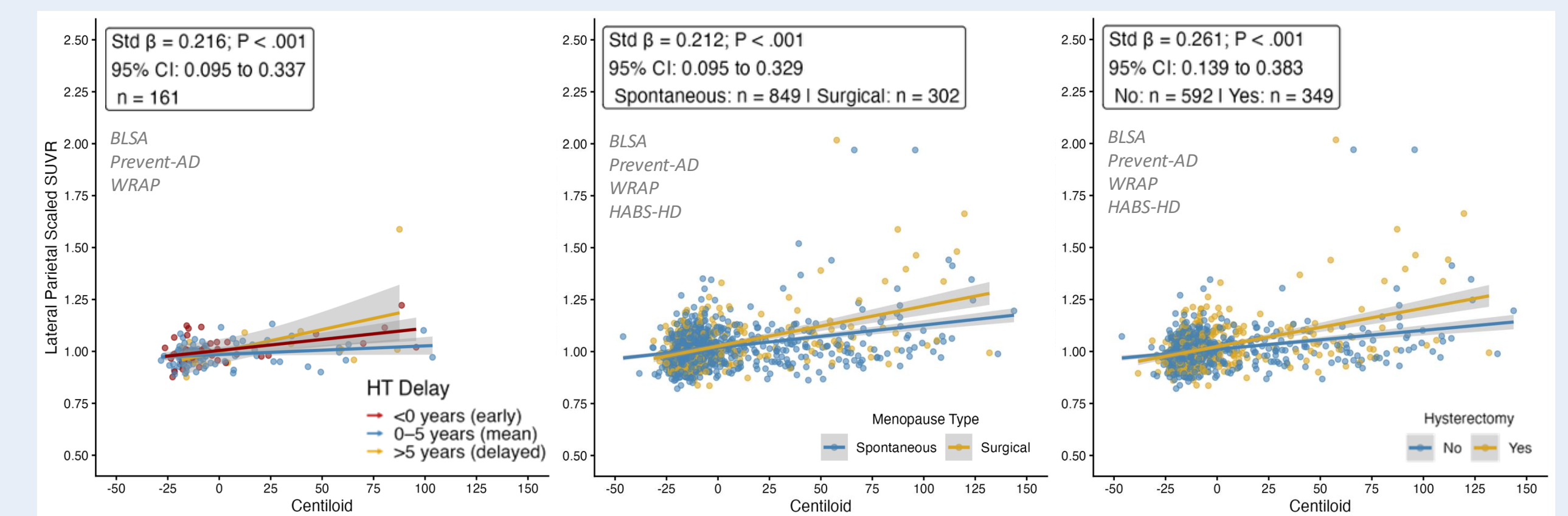


3. Faster neocortical tau accumulation in women with elevated amyloid and history of surgical menopause



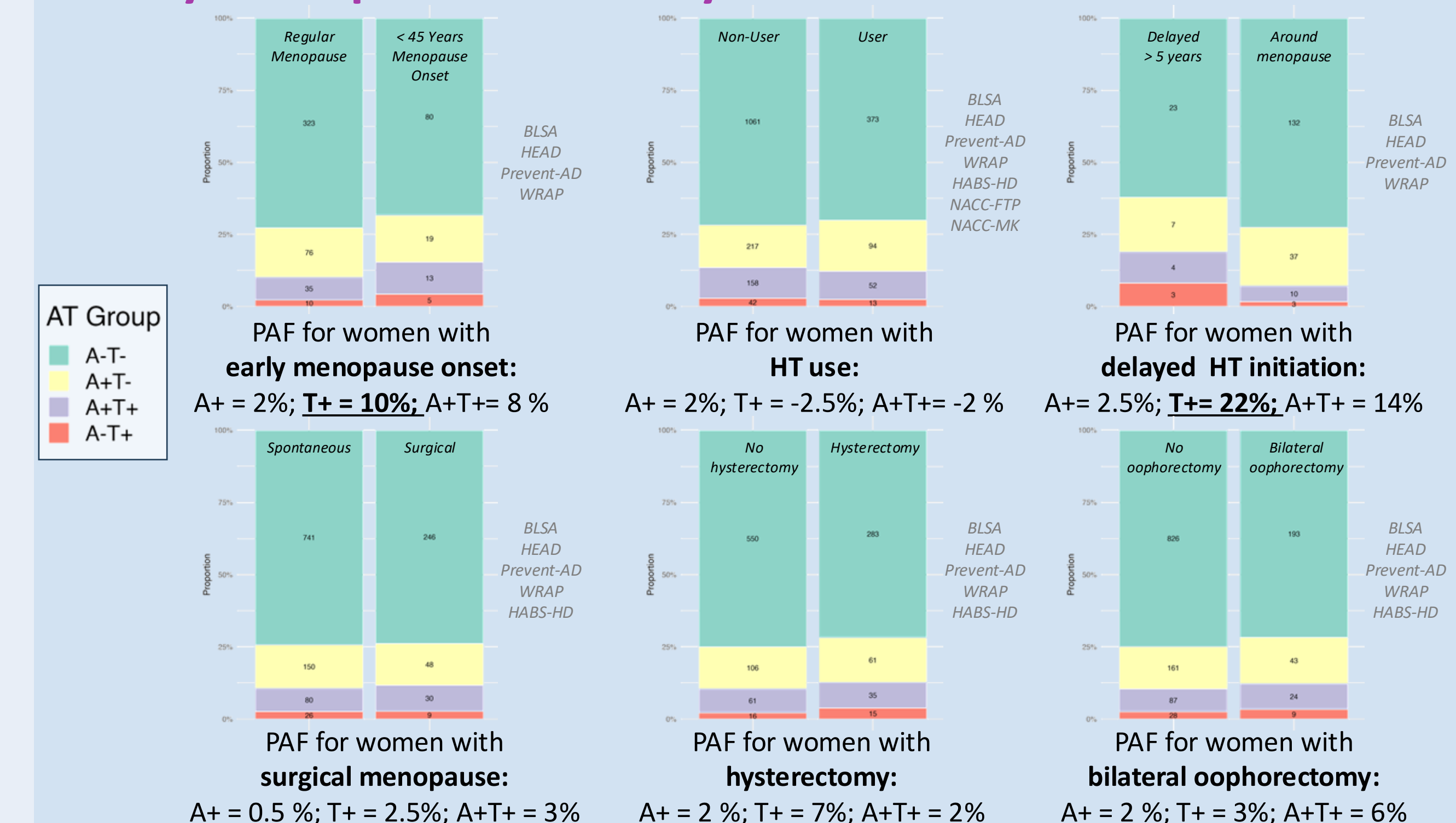
Results

2. Delayed initiation of HT and surgical intervention (specifically hysterectomy) associated with higher neocortical tau burden



* no significant effect found for menopause-onset-age & bilateral oophorectomy
** continuous pooled models corrected for age & cohort, and LMM additionally for time

4. Highest population attributable fractions (PAF) for AD biomarker positivity, in particular tau, in women with early menopause and delayed initiation of HT



Conclusion

- ✓ Amyloid-dependent effects of reproductive/endocrine factors predominantly observed for neocortical rather than medial temporal tau pathology
- ✓ Higher PAF associated with high tau in women with delayed hormone therapy initiation and earlier menopause onset, but no convincing difference in PAF for high amyloid
- ✓ Findings highlight contribution of female-specific reproductive/endocrine factors to AD biomarkers